13. (Amended) The method of claim 11, wherein the first antibody is immobilized on the solid support prior to contacting the first antibody with the test sample.

19. (Amended) The method of claim 1, wherein the second antibody binds to a different epitope of the surface array protein than does the first antibody.

20. (Amended) The method of claim 17, wherein the second antibody comprises a detectable label.

22. (Amended) A kit for detecting the presence or absence of *Bacillus anthracis* in a sample, the kit comprising:

a solid support upon which is immobilized a a first antibody that can specifically bind to a surface array protein (SEQ ID NO:1) of *Bacillus anthracis*; and

a second antibody which binds to the surface array protein.

25. (Amended) The kit of claim 22, wherein the first or second antibody is a recombinant polyclonal antibody.

27. (Amended) The kit of claim 22, wherein the first or second antibody is a mixture of monoclonal and polyclonal antibody preparations.

REMARKS

1. Status of the claims

Claims 2, 4, 17, 18, 24 and 30 are canceled. Claims 1, 5, 6, 7, 10, 11, 13, 19, 20, 22, 25 and 27 are amended. Claims 31-32 were withdrawn from consideration by the Examiner. Claims 1, 3, 5-16, 19-23 and 25-29 are pending and under consideration with entry of this Amendment.

2. Support for the Amendments

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted. No new matter is introduced by the Amendment.

A marked up copy of the amended claims are provided as Appendix A entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**" As a convenience to the Examiner, a complete set of the claims, as amended herein, is also attached to this Amendment as Appendix B.

3. Support for the Amendments

Applicants thank the Examiner for the helpful interview on September 3, 2002.

4. Rejections under 35 U.S.C. § 112, second paragraph

A. Claim 1

Claim 1 was rejected as allegedly vague in the recitation "detecting whether surface array protein is bound to the capture reagent." Specifically, the Examiner indicated that it was unclear how the surface array protein could be detected without a detection reagent.

Claim 1, as amended, includes the recitation "detecting whether the surface array protein is bound to the antibody with a second antibody that binds to the surface array protein." Since the second antibody plays the role of a detection reagent, Applicants submit that the amended claim is clear. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Claims 5-6

Claims 5-6 were rejected as allegedly vague in the recitation "recombinant." Specifically, the Examiner asked whether the term modified the antigen or antibody.

Applicants respectfully traverse the rejection. It is clear from the application that "recombinant antibodies" refer to antibodies that are recombinantly produced. *See, e.g.*, page 14, lines 5-19 of the specification. However, to expedite prosecution, claims 5-6 are amended to explicitly recite that the antibodies are recombinantly produced.

5. Rejections under 35 U.S.C. § 102

A. Ligler *et al*

Claims 1-4, 7, 8, 10, 11, 13-17, and 19-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ligler *et al.* Specifically, the Examiner argued that the claims as filed were inherently anticipated by Ligler *et al.* In addition, the Examiner noted that Ligler *et al.* discloses monoclonal antibody FDF-IB9. Applicants respectfully traverse the rejection.

As amended, claim 1 recites a method of specifically detecting a strain of *Bacillus anthracis* containing a surface array protein (SEQ ID NO:1) in a test sample, comprising contacting a test sample with a first antibody that can specifically bind to *Bacillus anthracis* surface array protein (SEQ ID NO:1), wherein the antibody forms a complex with the surface array protein if the surface array protein is present in the test sample; and detecting whether the surface array protein is bound to the antibody with a second antibody that binds to the surface array protein, wherein the presence of surface array protein is indicative of the presence of *Bacillus anthracis* in the test sample.

Ligler *et al.* does not teach or suggest using an antibody specific for SEQ ID NO:1 to detect *B. anthracis*. Monoclonal antibody FDF-IB9 is specific for "capsular material." *See*, column 8, lines 61-64 of Ligler *et al.* While it is not clear what the exact antigen recognized by the antibody is, it cannot be SEQ ID NO:1. Surface array protein is part of the S-layer of the bacteria, not the capsule. Therefore, FDF-IB9 does not specifically bind to SEQ ID NO:1. Since the amended claims require use of an antibody specific for SEQ ID NO:1, Ligler *et al.* cannot anticipate any of the cited claims.

In addition, claim 1, as amended, recites the use of two antibodies to detect anthrax. A first antibody is used to capture the surface array protein and a second antibody is used to detect the bound protein. Ligler *et al.* does not describe detecting proteins by capturing the protein on an antibody and then detecting the protein with a second antibody. Thus, the reference cannot anticipate the amended claims.

Moreover, claim 3 recites the method wherein the *B. anthracis* is encapsulated, i.e., wherein the bacteria is a spore. A review of Ligler *et al.* only provides an examination of expression in vegetative cells, not spores. Thus, Ligler *et al.* cannot anticipate claim 3.

Accordingly, withdrawal of the rejection is requested.

B. Yu *et al*

Claims 1-4, 7, 8, 10, 11, 13-17, and 19-21 were rejected as anticipated by Yu *et al.* Specifically, the Examiner argued that the claims as filed were inherently anticipated by Yu *et al.* Applicants respectfully traverse the rejection.

As amended, claim 1 recites the use of an antibody that can specifically bind to surface array protein (SEQ ID NO:1). Yu *et al.* describes two monoclonal antibodies specific for the *B. anthracis* spore itself. *See, e.g.*, section 3.1, describing detection of whole spores. As discussed above, the surface array protein is not expressed on the spore itself, but is part of the S-layer of the bacteria. Since the antibodies described in Yu *et al.* do not have the specificity of the antibodies recited in the amended claims, Yu *et al.* cannot anticipate the claims. Accordingly, Applicants respectfully request withdrawal of the rejection.

C. Graham *et al*

Claims 1-3 were rejected as allegedly anticipated by Graham *et al.* Applicants respectfully traverse the rejection.

Graham *et al.* describes the use of lectin-based molecules to detect *B. anthracis.* Lectins bind to carbohydrates, not protein. Therefore, the molecules

described in Graham *et al.* do not specifically bind to SEQ ID NO:1. Moreover, the amended claims are limited to antibodies. Graham *et al.* does not describe using antibodies to detect anthrax. Accordingly, Applicants respectfully request withdrawal of the rejection.

5. Rejections under 35 U.S.C. § 103

A. Rejection over Ligler *et al.* or Yu *et al.* in view of Litman *et al.*

Claims 1-30 were rejected under 35 U.S.C. § 103 as allegedly obvious over Ligler *et al.* or Yu *et al.* in view of Litman *et al.* Although the Examiner rejected claims 1-30, it appears that the rejection is only focused on the rejection of kit claims (claims 22-30). Specifically, the Examiner stated that the prior art does not teach reagent antibodies and detection reagents in the form of a kit, but that such a kit would be obvious in light of Litman *et al.* Applicants respectfully traverse the rejections.

A proper *prima facie* obviousness rejection must point out where each element of the claims is found in the prior art. As discussed above, neither Ligler *et al.* or Yu *et al.* describe an antibody that specifically binds to SEQ ID NO:1. As such, the references cannot anticipate or render the present claims obvious. The addition of Litman *et al.* does not cure this defect because Litman *et al.* does not teach or describe antibodies specific for SEQ ID NO:1. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Rejection over Phillips *et al.* in view of Toumelin *et al.*

Claims 1-21 were rejected under 35 U.S.C. § 103 as allegedly obvious over Phillips *et al.* in view of Toumelin *et al.* Specifically, the Examiner argued that Phillips teaches methods of raising antibodies against spore antigens and Toumelin *et al.* describes SEQ ID NO:1. The Examiner noted that Phillips *et al.* "suggest the investigation of antigen structure is advantageous in analyzing the spore antigens for diagnostic purposes." Therefore, the Examiner asserts that it would have been obvious to

use the methods of Phillips *et al.* to detect *B. anthracis* by detecting SEQ ID NO:1. Applicants respectfully traverse the rejection.

The disclosure of SEQ ID NO:1 and a general teaching that "spore antigens" can be used to detect anthrax is not sufficient to render the present claims obvious because there was no reasonable expectation that antibodies specific for SEQ ID NO:1 could be used to specifically detect *B. anthracis* and not, for instance, other common *Bacillus* strains. Moreover, Phillips *et al.* if anything, states that "spore antigens" should be investigated. As indicated previously, the surface array protein (SEQ ID NO:1) is part of the S-layer and would not be considered a "spore antigen." Thus, those of skill in the art would not have been motivated to combine the references as the Examiner suggests.

The disclosure of a protein sequence alone does not provide sufficient information to suggest that antibodies directed to that protein can specifically detect the organism that produces the protein. For example, an antibody directed to a *Bacillus anthracis* antigen may cross react with epitopes of related bacterial species, such as *B. cereus* or *B. thuringiensis*. Indeed, Phillips *et al.* points out that "[i]n diagnosing the disease anthrax, there are considerable problems in differentiating laboratory isolated of the causative agent, *Bacillus anthracis*, from other members of this genus that are widely distributed in the environment." *See*, page 169 of Phillips *et al.*, first sentence of introduction. Thus, there was a past history of cross reactivity of various detection reagents developed to detect anthrax. Cross reaction of prior art antibodies to common *Bacillus* strains made the antibodies useless for the detection of anthrax. The Examiner has not provided any reason to explain why those of skill in the art would have expected antibodies specific for the surface array protein to overcome this problem.

Phillips *et al.* only states that monoclonal antibodies may be useful to overcome cross-reactivity. Phillips *et al.* does not teach how to determine *a priori* which epitopes are likely to be present in other bacteria and which are not. It is only possible to determine that information by testing antibodies against common bacterial strains as are provided in the present application. Until antibodies specific for surface array protein are

tested for cross-reactivity, it is impossible to predict that surface array protein is a useful epitope to detect *B. anthracis*.

To the extent that Phillips *et al.* teaches anything, the reference teaches that "spore antigens" are useful for specific detection of anthrax. Indeed, Phillips *et al.* emphasizes that vegetative antigens seem to be the cause of the cross-reactivity with other *Bacillus* strains. S*ee, e.g.*, paragraph bridging pages 169-170 and the last paragraph on page 177 (stating that the epitope appears to be specific for spores as opposed to vegetative cells."). As indicated previously, surface array protein (SEQ ID NO:1) is part of the S-layer, i.e., it is part of *B. antrhracis* vegetative cells. Thus, if anything, Phillips *et al.* teaches away of using proteins such as the surface array protein as a target for detection reagents. Thus, the Examiner has not provided a *prima facie* obviousness rejection.

With regard to claim 3, there is no reason that those of skill in the art would expect to be able to detect anthrax spores using antibodies specific for the surface array protein. As discussed above, surface array protein is an S-layer protein, not a capsule protein. It is not predictable that an S-layer protein would be present in sufficient quantity in a spore preparation to detect its presence. Thus, the combined references do not render claim 3 obvious.

Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 273-7554.

Respectfully submitted,

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